Cardiovascular system

Lectures five and six

Thromboembolism and vasculitis

Objectives:

At the end of these two lectures, the students should be able to:

(1) Understand the basic pathology of thrombogenesis
(2) Risk factors for development of deep vein thrombosis.
(3) Know the types of embolus than can occur and the pathology of pulmonary embolism.
(4) Know the common causes of vasculitis with special emphasis on the clinic-pathological features and mechanism of:
    (A) Giant cell arteritis.
    (B) Polyarteritis nodosa.
    (C) Wegener's granulomatosis.
    (D) Cutaneous hypersensitivity vasculitis and Henoch Schonlein purpura

Key principles to be discussed:

(1) Pathological aspects of thrombogenesis: vessel wall abnormality, vascular stasis or turbulent flow and increased blood coagulability.
(2) Causes of embolism formation.
(3) Predisposing factors for deep vein thrombosis.
(4) Pathology of pulmonary thromboembolism.
(5) Brief description of other forms of emboli like: fat embolism, air embolism, atherosclerotic plaque embolism, amniotic fluid embolism, nitrogen embolism and infective endocarditis.
(6) Pathology of vasculitis: giant cell arteritis, polyarteritis nodosa, Wegener's granulomatosis, Henoch-Schonlein purpura and cutaneous hypersensitivity vasculitis.

Thromboembolism

Thrombosis:

A thrombus is a solid mass of blood constituents, which develops in artery or vein.

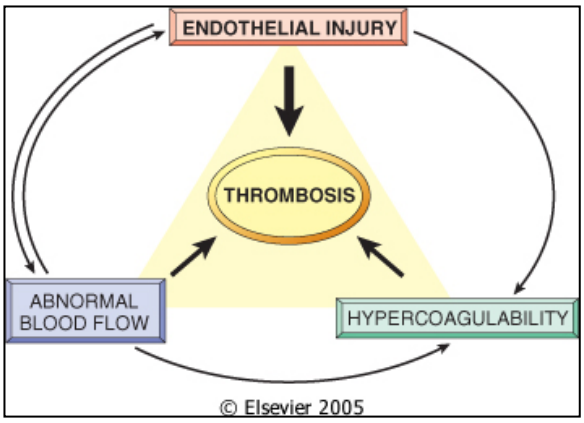
- It is intravascular coagulation of blood and it often causes significant interruption to blood flow.

Pathogenesis:

Three primary influences called as ***Virchow triad*** predispose to thrombus formation:

(1) Endothelial injury.
(2) Stasis or turbulence of blood flow.
(3) Blood hypercoagulability.

It results from interaction platelets, damaged endothelial cells and the coagulation cascade. All 3 are component of the hemostatic process.



Components of the hemostatic process:

1. Coagulation cascade (thrombotic) → Activation of platelets → Formation of thrombin → Fibrinogen → Fibrin
2. Fibrinolysis (Antithrombotic) → Activation of antithrombin 3, protein C and protein S → Generation of plasmin → Splits the fibrin.

Hypercoaguable States:

Can be

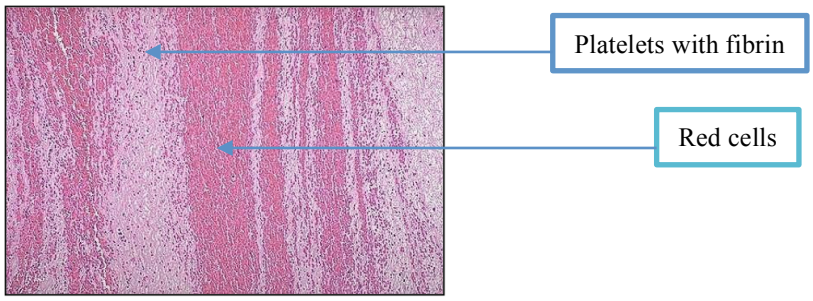
1. **Primary/Genetic:**
   E.g. mutation in factor V gene or prothrombin gene, anti-thrombin III deficiency, protein C or S deficiencies, or fibrinolysis defects.
2. **Secondary/acquired states:**
   a) **High risk for thrombosis**
      - Prolonged bed rest or immobilization
      - Myocardial infarction, Atrial fibrillation
      - Tissue damage (surgery, fracture, burns)
      - Cancer → release of procoagulant tumor products
      - Prosthetic cardiac valves
      - Disseminated intravascular coagulation→ thrombin generation.
      - Antiphospholipid antibody syndrome (lupus anticoagulant syndrome) → autoantibodies

   b) **Lower risk for thrombosis**
      - Cardiomyopathy
      - Nephrotic syndrome
      - Hyperestrogenic states (pregnancy)
      - Oral contraceptive use
      - Sickle cell anemia
      - Smoking.

Morphology of Thrombus:

- Thrombi may develop anywhere in the cardiovascular system, the cardiac chambers, valve cusps, arteries, veins, or capillaries.
- They vary in size and shape, depending on the site of origin.
- Arterial or cardiac thrombi usually begin at a site of endothelial injury (e.g., atherosclerotic plaque) or turbulence (vessel bifurcation)
- Venous thrombi characteristically occur in sites of stasis.
- The propagating tail of either thrombi may not be well attached (particularly in veins) is prone to fragmentation, creating an embolus.

Lines of Zahn:

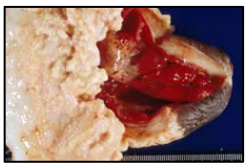
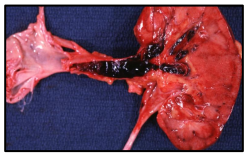


- A thrombus is made up of fibrin, platelets and RBC and few inflammatory cells.
- When formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations, called **lines of Zahn**.
- When arterial thrombi arise in heart chambers or in the aortic lumen they are termed **mural thrombi**.

Arterial thrombi	Venous thrombosis
• Most common sites in descending order, are coronary, cerebral, and femoral arteries. • It is usually superimposed on an atherosclerotic plaque and are firmly adherent to the injured arterial wall (mural). • Gray-white and friable.	• Also called **phlebothrombosis**, is almost invariably occlusive • The thrombus often takes the shape of the vein. • Because these thrombi form in a relatively static environment, they contain more enmeshed erythrocytes and are therefore known as red, or stasis thrombi. • Phlebothrombosis most commonly affects the veins of the lower extremities (90% of cases).

Postmortem Clots:

At autopsy, postmortem clots may be confused for venous thrombi.

Postmortem Clots	Venous thrombus
• Rubbery and gelatinous • Dark red in one side and yellow in the other. (gravity pulls RBCs down) • Not attached to the vessel wall	• Firm • Rich admixture of RBCs and appear red • Attached to the vessel wall • On transection reveal vague strands of pale gray fibrin.
	

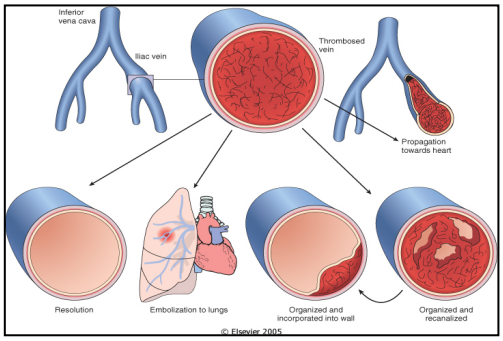
Thrombi on Heart Valves: (called as vegetations)

Can be:

1. Bacterial or fungal blood-borne infections may result in the development of large thrombotic masses on heart valves, called as vegetations (infective endocarditis).
2. Sterile vegetations can also develop on noninfected valves in patients with hypercoagulable states, so-called nonbacterial thrombotic endocarditis.
    - Less commonly, noninfective, verrucous (Libman-Sacks) endocarditis attributable to elevated levels of circulating immune complexes may occur in patients with systemic lupus erythematosus

Fates of Thrombus:

- Resolution
- Propagation
- Embolism
- Organization and recanalization
- Organization and incorporation into the wall



Thrombophlebitis and Phlebothrombosis:

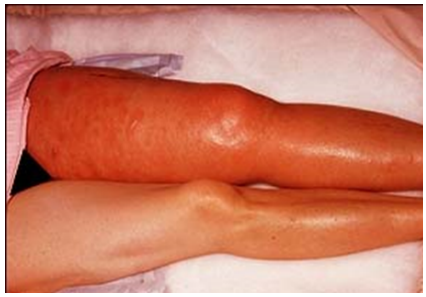
An inflammation in a vein with blood clot formation inside the vein itself at the site of inflammation.

Symptoms and signs:

Local manifestations include **edema**, **cyanosis**, **superficial vein dilation, heat, tenderness, redness, swelling**, and **pain**.

Deep vein thrombosis & Thrombophlebitis

- Venous thrombosis often arises in the deep veins of the legs and then it is called deep vein thrombosis (DVT).
- Such thrombi more often embolize to the lungs and give rise to pulmonary infarction.
- Can cause local pain and edema.
- DVTs are asymptomatic in approximately 50% of affected individuals and are recognized only in retrospect after embolization.



Common predisposing factors for DVT:

1. Bed rest and immobilization.
2. Congestive heart failure (a cause of impaired venous return).
3. Trauma, surgery, and burns.
4. Pregnancy:
    - The potential for amniotic fluid infusion into the circulation at the time of delivery can cause thrombogenesis
    - Late pregnancy and the postpartum period are also associated with systemic hypercoagulability
5. Tumors.
6. Advanced age.

Embolism:

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.

- Almost all emboli represent some part of a dislodged thrombus, hence the commonly used term thromboembolism.
- The emboli ultimately lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion leading to ischemic necrosis of distal tissue (infarction).
- Depending on the site of origin, emboli may lodge in the pulmonary or systemic circulations.

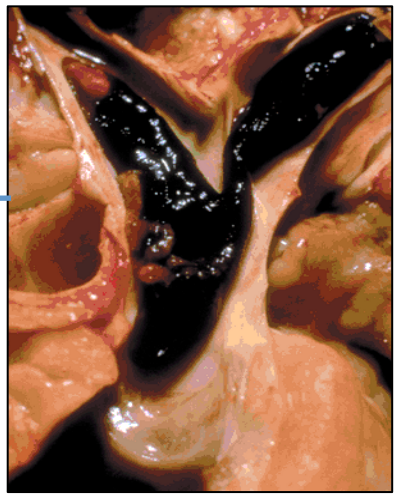
Types of Embolism:

- Pulmonary thromboembolism
- Systemic thromboembolism
- Fat embolism
- Air embolism
- Amniotic fluid embolism

Pulmonary thromboembolism:

Usually the thrombus fragments in DVTs and get carried by blood to pass through the right side of the heart.. then it arrest at the pulmonary vasculature.

- In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee
- Depending on size of embolus, it may occlude main pulmonary artery, or impact across the bifurcation (saddle embolus), or pass out into the smaller, branching arterioles of the pulmonary circulation.



- Most pulmonary emboli (60% to 80%) are clinically silent because they are small. Sudden death, right heart failure (cor pulmonale), occurs when 60% or more of the pulmonary circulation is obstructed with emboli.
- Embolization in the pulmonary circulation leads to hypoxia, hypotension, and right-sided heart failure.
- Rarely, an embolus passes through an atrial or ventricular defect and enters the systemic circulation (*paradoxical embolism*).
- Embolic obstruction of small end-arteriolar pulmonary branches may result in infarction.

Systemic Thromboembolism:

- Refers to emboli traveling within the arterial circulation.
- Most (80%) arise from intracardiac mural thrombi.
- The major sites for arteriolar embolization are the lower extremities (75%) and the brain (10%)
- Arterial emboli usually cause infarction of tissues supplied by the artery

  (The consequences of systemic emboli depend on the extent of collateral vascular supply in the affected tissue, the tissue's vulnerability to ischemia, and the caliber of the vessel occluded).

Fat Thromboembolism:

- Microscopic fat globules may be found in the circulation after **fractures of long bones** (which have fatty marrow) or, rarely, in soft tissue trauma and burns.
- Fat is released by marrow or adipose tissue injury and enters the circulation through rupture of the blood vessels and act as an embolus.
- **Fat embolism syndrome** is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia.

Air Embolism:

- Gas bubbles within the circulation can obstruct vascular flow (and cause distal ischemic injury) acting as thrombotic masses. Bubbles may coalesce to form frothy masses sufficiently large to occlude major vessels.
- Air may enter the circulation during ***obstetric procedures*** or as a consequence of ***chest wall injury***.
- An excess of 100 cc is required to have a clinical effect.

Decompression Sickness: A particular form of ***gas embolism***

- Occurs when individuals are exposed to ***sudden changes in atmospheric pressure***.
- Scuba and deep sea divers, and individuals in unpressurized aircraft in rapid ascent are all at risk.
- When air is breathed at high pressure (e.g. during a deep sea dive), increased amounts of gas (particularly nitrogen) become dissolved in the blood and tissues. If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues and bubbles out of solution in the blood to form gas emboli.
- '***Grecian Bend***' i.e. joint/muscle pain and 'chokes' i.e. respiratory distress.
- A more chronic form of decompression sickness is called *caisson disease* in which, persistence of gas emboli in the skeletal system leads to multiple foci of ischemic necrosis; the more common sites are the heads of the femurs, tibia, and humeri.

Amniotic Fluid Embolism:

- A grave and uncommon complication of ***labor and the immediate postpartum period***, caused by infusion of amniotic fluid or fetal tissue into the maternal circulation via a tear in the placental membranes or rupture of uterine veins.
- Characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma.
- If the patient survives the initial crisis, pulmonary edema develops, along with disseminated intravascular coagulation, owing to release of thrombogenic substances from amniotic.
- Microscopy:

  Presence in the pulmonary microcirculation of squamous cells shed from fetal skin, lanugo hair, fat from vernix caseosa, and mucin derived from the fetal respiratory or gastrointestinal tract. Marked pulmonary edema and diffuse alveolar damage are also present. Systemic fibrin thrombi indicative of DIC can also be seen.

Vasculitis

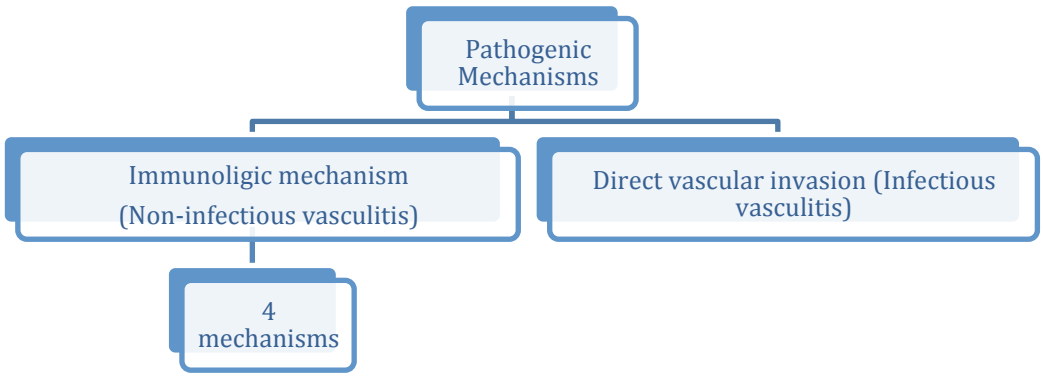
Definition: It is inflammation of vessel walls with many possible symptoms

Infectious Vasculitis: (Read it)

Localized arteritis may be caused by the direct invasion of arteries by infectious agents, usually bacteria or fungi, and in particular *Aspergillus*and *Mucor*spp. Vascular invasion can be part of a more general tissue infection (e.g., bacterial pneumonia or adjacent to abscesses), or—less commonly— arise from hematogenous spread of bacteria during septicemia or embolization from infective endocarditis.

The two most common pathogenic mechanisms of vasculitis are:

- Immune-mediated **inflammation** → *Immunosuppressive therapy* is ***appropriate***
- Direct vascular invasion by **infectious** pathogens → *Immunosuppressive therapy* ***exacerbates*** infectious vasculitis



Infections also can indirectly precipitate[1] immune-mediated vasculitis (e.g., by generating immune complexes or triggering cross- reactivity).

Noninfectious Vasculitis (immunologic vasculitis):

Pathogenesis and Causes:

It is usually immune-mediated. The main immunologic mechanisms underlying noninfectious vasculitis are:

- **Immune complex deposition:**

  Seen in immunologic disorders such as systemic lupus erythematosus that is associated with *autoantibody production*. Immune complex deposition is implicated in the following vasculitides:

  - Drug hypersensitivity vasculitis:
    - E.g., penicillin
    - Skin lesions are most common
    - Discontinuation of the offending agent usually leads to resolution.
  - Vasculitis secondary to infections:

    Antibody to microbial constituents can form immune complexes that circulate and deposit in vascular lesions. In up to 30% of patients with polyarteritis nodosa, the vasculitis is attributable to immune complexes composed of hepatitis B surface antigen (HBsAg) and anti-HBsAg antibody.

[1] To happen suddenly, unexpectedly, or prematurely

❖ **Antineutrophil cytoplasmic antibodies (ANCAs):**

Patients with vasculitis have antibodies that react with neutrophil cytoplasmic antigens, called anti-neutrophil cytoplasmic antibodies (ANCAs). ANCAs are directed against the enzymes of neutrophil primary granules, monocyte lysosomes, and endothelial cells.

Two are most important:

- Antiproteinase-3 (PR3-ANCA) or (C-ANCA). Associated with Wegener granulomatosis.
- Anti-myeloperoxidase (MPO-ANCA) or (P-ANCA). Associated with microscopic polyangiitis.

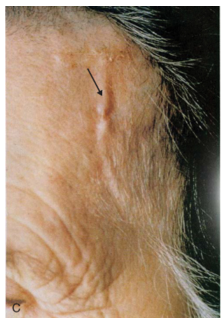
❖ **Anti-endothelial cell antibodies:**

These are anti-bodies to endothelial cells that underlie certain vasculitides

❖ **Autoreactive T cells**

❖ **It can also be caused by infection.**

Giant-Cell (Temporal) Arteritis:



- Most common type of vasculitis
- Patients >50, F: M = 2:1.
- Chronic, granulomatous inflammation of large to small arteries, especially in head particularly the branches of the carotid artery (temporal a. and branches of the ophthalmic a.)
- Involvement is segmental, acute and chronic.

Clinical Features:

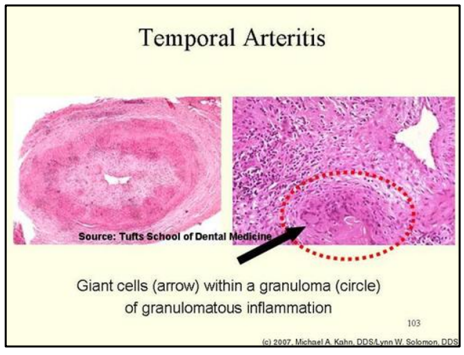
- Symptoms:
  - + Fever, weight loss, facial pain or headache, often most intense along the course of the superficial temporal artery.
  - + Thickened and painful temporal artery
  - + Jaw pain
  - + Visual problems and acute vision loss

Ophthalmic artery involvement can lead to sudden and permanent blindness.

- The diagnosis depends on biopsy and histologic confirmation.
- Treatment: corticosteroids or anti-TNF therapies

Morphology:

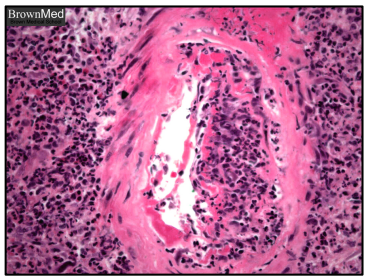
- Granulomatous inflammation of the blood vessel wall.
- Giant cells.
- Disruption and fragmentation of internal elastic lamina.
- The healed stage reveals collagenous thickening of the vessel wall and the artery is transformed into a fibrous cord.
- Infiltrate of lymphocytes and macrophages, with multinucleate giant cells.
- Nodular intimal thickening (and occasional thrombosis) that reduce the lumen diameter and cause distal ischemia.



Polyarteritis Nodosa:

- Cutaneous only or systemic.
- Disease of young adults.
- There is segmental necrotizing inflammation of arteries of medium to small size, in any organ (especially kidney and skin) except the lung.
- Polyarteritis nodosa has been associated with hepatitis B or hepatitis C.
- Clinical manifestations result from ischemia and infarction of affected tissues and organs, and are:
  - Fever
  - Weight loss
  - Abdominal pain and melena (bloody stool)
  - Muscular pain and neuritis.
  - In young-adults → Hypertension because of renal involvement.
  - Skin lesions associated with HBsAg.
- Renal arterial involvement is often prominent and is a major cause of death.
- Particularly characteristic of PAN is that all the different stages of activity (i.e. active and chronic stages) may coexist in same artery or in different vessels at the same time.
- Treatment: Corticosteroid or anti-TNF therapies
- Fatal if untreated, but steroids and cyclophosphamide are curative.

Morphology:



- Segmental inflammation
- Fibrinoid necrosis
- Occlusion of the lumen of this artery.
- Note that part of the vessel wall at the left side is uninvolved.

- In the acute phase:

  Transmural mixed inflammatory infiltrate, frequently accompanied by fibrinoid necrosis and luminal thrombosis

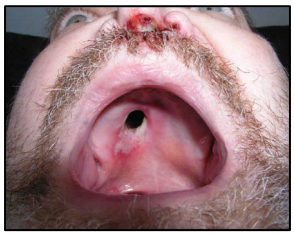
- Older lesions: Fibrous thickening of the vessel wall extending into the adventitia

- All stages of activity:

  (From early to late) coexist in different vessels or even within the same vessel, suggesting ongoing and recurrent pathogenic insults.

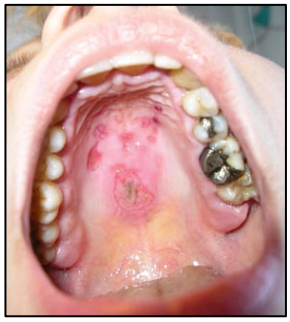
Wegener granulomatosis:

- A necrotizing vasculitis characterized by the triad of:
  1) Necrotizing granulomas of the upper and lower respiratory tract
  2) Necrotizing or granulomatous vasculitis of small to medium-sized vessels
  3) Renal disease in the form of necrotizing, crescentic, glomerulonephritis.
- Males are affected more often than females, at an average age of about 40 years.
- C-ANCAs (PR3-ANCAs) (antineutrophilic cytoplasmic antibodies) is positive in serum of more than 95% of patients.



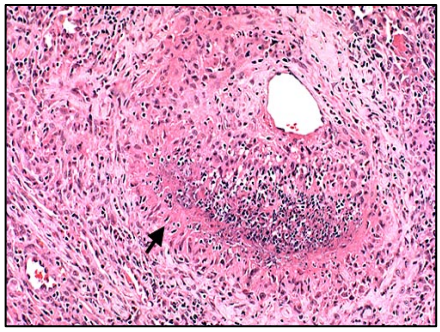
Palatal Destruction

- Clinical presentation:
  - Persistent pneumonitis
  - Chronic sinusitis
  - Mucosal ulcerations of the nasopharynx
  - Evidence of renal disease.
- Treatment: steroids, cyclophosphamide, TNF inhibitors and anti–B cell antibodies (Rituximab)
- Untreated: fatal - may lead to death within 2 years if not treated.



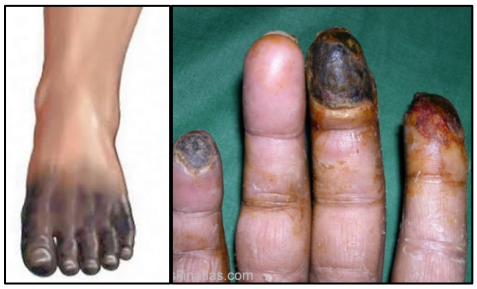
Palatal ulceration

Morphology:



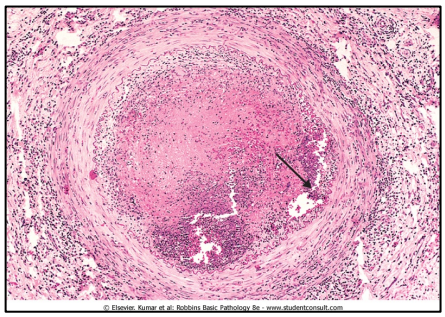
- Collection of epithelioid histiocytes = granuloma
- Fragmented smooth muscle
- Destroyed blood vessel by inflammation
- URT Lesions:
  Necrotizing granulomatous vasculitis with a surrounding fibroblastic proliferation.
- Renal Lesions:
  - → Focal and segmental necrotizing glomerulonephritis.
  - → Epithelial crescents (crescentic glomerulonephritis).

Thromboangiitis obliterans (Buerger disease):



- Medium-sized and small arteries,
- Leg and hands. (specially tibial and radial arteries)
- Heavy smokers of cigarettes, before age 35.
- Tobacco either leads to direct toxicity to endothelium, or indices an immune response
- Pain in the affect hand or foot induced by exercise (called *instep claudication*).
- Patients tend to have pain even at rest, due to the neural involvement. Chronic ulcerations of the toes, or fingers may appear, followed in time by gangrene.
- Abstinence from cigarette smoking in the early stages of the disease brings relief from further attacks

Morphology:



Microscopically, there is acute and chronic inflammation, accompanied by luminal thrombosis.

The inflammatory process extends into adjacent veins and nerves (rare with other forms of vasculitis), and in time all three structures become encased in fibrous tissue.

Cutaneous leukocytoclastic or hypersensitivity vasculitis (angiitis):

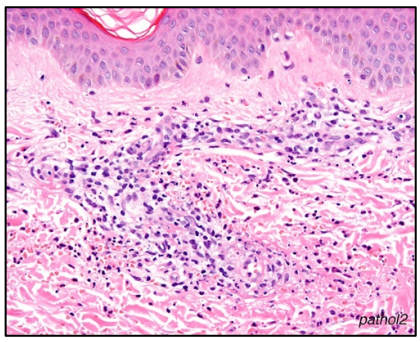
- Necrotizing vasculitis of arterioles, capillaries, and venules.
- Can be cutaneous only or systemic
- Is inflammation of small blood vessels (usually post-capillary venules in the dermis),
- Characterized by palpable purpura.
- The most common vasculitis seen in clinical practice.
- Leukocytoclasis = (karyorrhexis of neutrophils) in and around the vessels.
- It affects many organs e.g. Skin (most common), mucous membranes, lungs, brain, heart, GI, kidneys and muscle.

Causes:

- Idiopathic
- Immunologic reaction to an antigen that may present as
  - Drugs e.g. penicillin
  - Infectious microorganisms e.g. Strept. And other infections.
  - Food products and toxic chemicals
  - Tumor antigens in various cancers.
- It may be a part of a systemic disease:
  - Collagen vascular diseases (lupus erythematosus, rheumatoid arthritis).
  - Henoch-Schonlein purpura.
  - Why is it important to link vasculitis to its specific disorder?

    Because of they have important therapeutic implications, Example: lupus vasculitis and antiphospholipid antibody syndrome can share morphologic features, the former requires anti-inflammatory therapy while anticoagulation is indicated in the latter.

Morphology:



- Skin biopsy is often diagnostic.
- Histologically there is infiltration of vessel wall with neutrophils, which become fragmented called as leukocytoclasia or nuclear dust.
- Extra vasated RBCs.
- Fragmentation of neutrophil nuclei in and around vessel walls.

Henoch-Schonlein purpura (HSP):

- HSP is an IgA-mediated, autoimmune systemic small vessel hypersensitivity vasculitis of childhood.
- It causes skin purpura, arthritis, abdominal pain, gastrointestinal bleeding, orchitis and nephritis.
- The aetiology remains unknown.
- Immunoglobulin A (IgA) and complement component 3 (C3) are deposited on arterioles, capillaries, and venules.
- Serum levels of IgA are high in HSP.

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قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة

دعواتنَا لكم بالتوفيق.